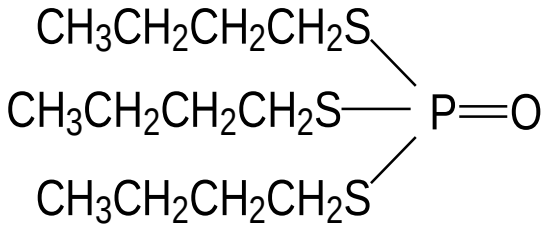
EVALUATION OF S,S,S-TRIBUTYL PHOSPHOROTRITHIOATE (DEF) AS A TOXIC AIR CONTAMINANT



Executive Summary

(Including the Findings of the Scientific Review Panel)

California Department of Pesticide Regulation

California Environmental Protection Agency
Sacramento, California

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California Environmental Protection Agency
Department of Pesticide Regulation

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Preface

Assembly Bills 1807 and 3219 established a procedure for the identification and control of toxic air contaminants (TAC) in California. Under these laws, the Department of Pesticide Regulation (DPR) has the responsibility to determine whether pesticides may be TACs. Once a pesticide has been identified as a TAC, DPR is required to determine, in consultation with the Office of Environmental Health Hazard Assessment, the Air Resources Board, the air pollution control districts, and air quality management districts of the affected counties, the need for and appropriate degree of control measures (§ 14021 et seq., Food and Agricultural Code). As part of the identification process, DPR is required to prepare a report documenting the airborne concentrations of a candidate TAC, and to evaluate whether these concentrations are a present or potential hazard to human health.

In preparing this report, staff reviewed pertinent scientific literature through October 1997.

EXECUTIVE SUMMARY

Introduction

This report was developed in accordance with provisions of the state law (Food and Agricultural Code Title 3, Division 1.5, sections 14020–14027) which became effective January 1984. This legislation specifies a two-phase process for the evaluation and control of pesticides, separating risk assessment (identification of a pesticide as a TAC) from risk management (mitigation of exposure to pesticides that have been identified as TACs). During the identification phase, a report is developed that evaluates the potential for developing human adverse health effects of a pesticide that may be, or is, emitted into air in California, and whether that pesticide is found in community air of California.

Following completion of this report, DPR's Director decides whether or not the pesticide should be identified as a TAC. If the pesticide has not been identified in community air of California, the Director may still declare the pesticide a TAC if adverse health effects exist, and if the pesticide has been documented in air outside of California under environmental conditions similar to those found in California. Upon identification, the pesticide is listed by regulation as a TAC in Title 3 of the California Code of Regulations and enters the mitigation phase.

What is contained in this report?

This report evaluates the potential of S,S,S–tributyl phosphorotrithioate (DEF) to be a TAC and includes:

- a review of the available scientific evidence on DEF regarding its physical properties, environmental fate, and human health effects;
- results documenting ambient airborne concentrations of DEF as well as results documenting air concentrations following an application;
- an estimate of human exposure to DEF in air;
- an assessment of the risk to humans resulting from current or anticipated exposures to airborne DEF.

What is DEF and how is it used?

DEF 6® and Folex 6EC® are product names for the active ingredient S,S,S–tributyl phosphorotrithioate. In this report, we refer to both products as "DEF."

DEF is a clear, colorless to pale amber liquid with a melting point of –25°C, a boiling point of 150°C (at 0.3 mm Hg), and a vapor pressure of 1.7×10^{-6} mm Hg at 20°C. Readily soluble in most organic solvents, DEF is formulated as an emulsifiable concentrate. DEF has an organophosphate chemical structure with a molecular formula of $(CH_3CH_2CH_2CH_2S)_3P{=}O$. DEF is designated as a toxicity Category I (Danger) restricted use pesticide.

Used solely as a cotton defoliant, growers apply DEF to cotton plants just before harvest to accelerate desiccation of the plants. Defoliation is preferable because green leaves remaining on cotton plants lead to clogged picking equipment and stained cotton fibers. Approximately 80 percent of all DEF applications are made aerially; the remaining 20 percent are made by ground.

The amount of DEF used has remained steady in recent years. From 1987 through 1995, the amount of DEF used annually ranged from 775,935 lb to 1,034,857 lb applied on 574,628 ac to 659,152 ac. Average rates for those years ranged from 1.34 lb/ac to 1.70 lb/ac. Over 90 percent of DEF is sprayed during September and October. From 1990 through 1995, over 95 percent of DEF was applied within the Central Valley counties of Fresno, Kings, Kern, Merced, Madera, and Tulare. Approximately half of this amount was applied within Fresno County. In 1995, DEF was used to defoliate 47% of all cumulative cotton acreage.

What is the fate of DEF in the environment?

The presence of DEF in ambient air is the result of its application and volatilization from foliar and soil surfaces. In the presence of light, DEF converts to n-butyl mercaptan and n-butyl disulfide. These reactions generally occur within 24 hours.

What are the reported concentrations of DEF and n-butyl mercaptan in air in California?

As requested by DPR, the Air Resources Board (ARB) contracted with investigators in the Department of Environmental Toxicology at the University of California, Davis (UCD) to conduct air sampling for DEF; samples were analyzed by ARB's laboratory. The UCD investigators monitored ambient airborne levels of DEF in the southern San Joaquin Valley at four rural sites in Fresno County (Tranquility, San Joaquin, Five Points, and Huron) during peak application time in September and October. Concurrent urban background samples were collected in Fresno (Fresno County) and Bakersfield (Kern County).

The highest 24-hour average concentration for positive samples of DEF was 26.4 parts per trillion (ppt) (340.0 ng/m^3) at Five Points, followed by 16.0 ppt (206.0 ng/m^3) at Tranquility and 15.4 ppt (196.5 ng/m^3) at San Joaquin. The percentage of samples above the minimum detection level (MDL) of 0.1 ppt at each site was 97 percent, 94 percent, and 91 percent, respectively. The maximum positive background level in Fresno was 0.4 ppt (5.4 ng/m^3) and 0.9 ppt (11.8 ng/m^3) in Bakersfield, although 80% or more of the samples were below the MDL at both monitoring sites. The average concentration for all samples collected from Five Points, Tranquility, and San Joaquin, including samples below the MDL, was 8.4, 5.4, and 3.6 ppt (107.3, 69.7, 46.0 ng/m^3) respectively.

Concentrations of DEF in air reported in the literature represent two types of monitoring—application and ambient. Three studies, using sampling equipment placed downwind from the application site, quantified airborne levels of DEF at specific intervals after spraying. One of the studies, in Kern County, estimated that one-tenth to one-half of the sprayed DEF missed the cotton plants and reached the ground, where it would volatilize over time. In a second study, in Fresno County, downwind concentrations of DEF four hours after application were 145.4 ppt and 52.8 ppt at 45 m and 350 m from the application site, respectively. The third application monitoring study took place in two fields in Kings County. The researcher monitored concentrations of DEF, n-butyl disulfide, and n-butyl mercaptan. In the first field, most DEF and n-butyl mercaptan were collected downwind immediately following application. Levels of n-butyl mercaptan higher than trace amounts were recovered at 24 h (upwind) and 96 h (downwind) following application. In the other field, most n-butyl mercaptan was collected two and 24 hours after application by samplers placed 10 m downwind.

Two of the five ambient monitoring studies reported maximum levels of DEF of 1.3 ppt around Stoneville, Mississippi. The researchers correlated the highest concentrations with reported spraying and the lowest concentrations with several days of rain. The other three studies measured concentrations of DEF in the San Joaquin Valley during the peak application season. The first of these studies monitored DEF in Fresno, Merced, Kings, and Madera counties. Levels of DEF ranged from zero to 0.03 ppt (Madera County). In the second study, airborne levels of DEF were monitored but not detected at two schools in Madera and Merced counties. The third study monitored DEF at ten rural and urban sites in Kern County. During peak application time in early October, DEF was detected at all sites; evening samples at two sites showed higher concentrations than did morning samples. The highest concentrations of DEF was 4.1 ppt during peak application time, and 6.9 ppt one week after application.

Data from both application and ambient monitoring studies show that levels of DEF and n-butyl mercaptan are highly variable during the peak application season depending on wind conditions and weather patterns. Some of the studies indicate that detectable amounts of DEF remain near the application site and may move to inhabited areas up to four to seven days following application.

What are the expected exposures to airborne concentrations of DEF and n-butyl mercaptan and when do these exposures occur?

Residents of rural and urban communities near cotton fields treated with DEF are potentially exposed to airborne residues during the harvest season. Monitoring data from ambient air in residential areas interfacing with cotton-growing regions of California were used to estimate public exposure to DEF. Exposure was calculated as an absorbed dose per unit of body weight for children, adult males, and adult females. An inhalation absorption rate of 100 percent was

assumed. Children of age six years were chosen as the highest exposure subgroup because they have the highest inhalation rate to body weight ratio during rest and light activity.

Because the level of exposure to airborne DEF depends on the rate of inhalation, and rate of inhalation varies with human activity, the estimate of exposure for children, adult males, and adult females was obtained from each group's inhalation rate during various daily (24 hours) activities. The estimate of a single day of acute exposure to a person was expressed as the absorbed daily dosage (ADD). The 95th percentile of the airborne DEF concentrations at each location during the entire season was used to calculate a single day's exposure. Seasonal exposure to a person is expressed as seasonal average daily dosage (SADD). The mean airborne DEF level during the entire season at each location was used to calculate a SADD. A seasonal exposure period of 60 days in a year was used to calculate annual exposure or annual average daily dosage (AADD).

Data from a study conducted in Fresno County showed a peak exposure period from mid-September to mid-October with significant exposure during the entire months of September and October. The estimates of ADD for residents of cotton-growing areas in Fresno County ranged from 24 to 304 ng/kg/day. SADD ranged from 9 to 123 ng/kg/day and AADD ranged from 2 to 20 ng/kg/day. Children consistently had the highest estimates of exposure per unit of body weight followed by male adults.

Data from a second study conducted in Kern County did not show daily airborne DEF concentrations during the entire defoliation season. However, the pre- and post-application data suggest an exposure period starting in mid-September and ending in early November with a peak exposure period throughout the month of October. The two-month seasonal exposure is consistent with the data collected in Fresno County. The estimates of ADD for residents of rural Kern County cotton-growing areas and urban Bakersfield ranged from 16 to 52 ng/kg/day and from 9 to 30 ng/kg/day, respectively. The SADD for residents of rural Kern County and urban Bakersfield areas ranged from 7 to 23 ng/kg/day and from 5 to 17 ng/kg/day, respectively. The AADD ranged from 1 to 4 ng/kg/day for residents of rural Kern County and 1 to 3 ng/kg/day for residents of urban Bakersfield. Again, children were the subgroup with the highest exposure per unit of body weight in all areas followed by male adults.

Both adults and children spent more than 85 percent of their day indoors. The public exposure to DEF was estimated assuming the DEF concentration is the same indoors and outdoors. This assumption may provide a several-fold overestimation of exposure since studies have shown that the indoor ambient concentrations of tested volatile organic chemicals were up to eight-fold less than outdoor concentrations of these chemicals.

In a third study conducted in the San Joaquin Valley, ambient air in Coalinga (Fresno County), Dos Palos (Merced County), Lemoore (Kings County), and Mendota (Madera County) was

monitored for DEF and n-butyl mercaptan from October 1 through November 2, 1980. All applications within one mile of these monitoring sites were made using ground equipment—except in Mendota, where aerial applications were made nearby. Some information such as MDL, type of sampling media, and efficiency of sampling media was missing in this report and only positive samples for n-butyl mercaptan concentrations were reported. DEF concentration ranged from nondetectable to 0.4 ng/m^3. Only 6 percent of the samples taken and analyzed instantly were positive for n-butyl mercaptan. Daily average concentration of n-butyl mercaptan for positive samples ranged from 1.9 µg/m^3 to 28.6 µg/m^3. Concentration of n-butyl mercaptan showed no clear pattern over time either in a single location (Dos Palos) or in all locations combined.

What are the potential acute and chronic non-carcinogenic health effects of DEF?

The primary health effects of DEF after an acute (~one day) exposure are due to the inhibition of various enzymes in the nervous system including cholinesterase (ChE) and neuropathy target esterase (NTE). In animals, acute inhalation exposure to DEF produced not only cholinergic signs (pupil constriction, diarrhea, excessive tearing, excessive salivation, twitching, tremors, convulsions) and delayed neuropathy (loss of coordination, paralysis), but also respiratory distress (slow or irregular breathing, red nasal passages) and general signs of malaise (reduced activity, ungroomed and/or erect fur). Additional health effects seen with acute exposure by other routes included reduced body temperatures and anemia. A variety of symptoms have been reported in humans that have been attributed to exposure to DEF including eye and throat irritation, various respiratory effects, excessive salivation, nausea, vomiting, headache, diarrhea, muscle weakness, fatigue, pupil constriction, and dizziness. The no-observed-effect level (NOEL) selected for evaluating acute exposure was 12.2 mg/m^3 (2.9 mg/kg) based on reduced activity, slow or irregular breathing, ungroomed and/or erect fur, increased vocalization, and increased startle response in rats exposed to DEF at 59.5 mg/m^3 (14.3 mg/kg) for six hours per day.

When animals were exposed to DEF by the inhalation route for periods ranging from three weeks to three months, additional effects were seen including reduced body weights and food consumption, impaired retinal response, and microscopic changes to the retina and adrenal glands. Several reproductive effects were seen in rats including reduced fertility, increased gestation length, increased number of stillbirths, reduced birth weights, increased postnatal deaths, and discolored livers in offspring. The NOEL selected for evaluating seasonal exposure was 12.2 mg/m^3 (2.9 mg/kg/day) based on clinical signs, brain ChE inhibition, anemia, impaired retinal response, and microscopic lesions in the retina and adrenal glands of rats exposed to DEF at 59.5 mg/m^3 (14.3 mg/kg/day) for six hours per day, five days per week for 13 weeks.

Is there any potential cancer risk from exposure to DEF?

An increase in tumors of the small intestine (adenocarcinomas in both sexes), the liver (hemangiosarcomas in males), and the lung (alveolar/bronchiolar adenomas in females) was seen in a study where mice were administered DEF in the diet for 90 weeks. The increase in tumors

was only observed at the highest dose level in the small intestine and lungs; however, the incidence of the liver tumors in males was increased at both the mid- and high-dose level. Based on the incidence of liver tumors in male mice, the estimated cancer potency of DEF ranged from 4.7×10^{-2} (maximum likelihood estimate) to 8.4×10^{-2} (95 percent upper bound estimate) $(mg/kg/day)^{-1}$ after adjusting for oral absorption. The estimated cancer potency for DEF expressed as unit risk is shown in Table 1 relative to other chemicals for which there are cancer potency estimates that have been approved by the Scientific Review Panel for Toxic Air Contaminants. The unit risk estimate for DEF ranged from 9.2×10^{-6} $(\mu g/m^3)^{-1}$ for the MLE to 1.6×10^{-5} $(\mu g/m^3)^{-1}$ for the 95% UB. No increase in tumors was observed in rats. All of the available genetic toxicity studies for DEF were negative.

Table 1. Cancer Potency for DEF Relative to Other Oncogenic Potencies Approved by the Scientific Review Panel for Toxic Air Contaminants

Compound	Unit Risk $(\mu g/m^3)^{-1}$	Range $(\mu g/m^3)^{-1}$
Dioxins	3.8×10^{1}	2.4×10^{1} to 3.8×10^{1}
Chromium IV	1.5×10^{-1}	1.2×10^{-2} to 1.5×10^{-1}
Cadmium	4.2×10^{-3}	2.0×10^{-3} to 1.2×10^{-2}
Inorganic Arsenic	3.3×10^{-3}	6.3×10^{-4} to 1.3×10^{-2}
Benzo[a]pyrene	1.1×10^{-3}	1.1×10^{-3} to 3.3×10^{-3}
Diesel Exhaust	3×10^{-4}	1.3×10^{-4} to 2.4×10^{-3}
Nickel	2.6×10^{-4}	2.1×10^{-4} to 3.7×10^{-3}
1,3-Butadiene	1.7×10^{-4}	4.4×10^{-6} to 3.6×10^{-4}
Ethylene Oxide	8.8×10^{-5}	6.1×10^{-5} to 8.8×10^{-5}
Vinyl Chloride	7.8×10^{-5}	9.8×10^{-6} to 7.8×10^{-5}
Ethylene Dibromide	7.1×10^{-5}	1.3×10^{-5} to 7.1×10^{-5}
Carbon Tetrachloride	4.2×10^{-5}	1.0×10^{-5} to 4.2×10^{-5}
Benzene	2.9×10^{-5}	7.5×10^{-6} to 5.3×10^{-5}
Ethylene Dichloride	2.2×10^{-5}	1.3×10^{-5} to x 2.2×10^{-5}
DEF	1.6×10^{-5}	9.2×10^{-6} to 1.6×10^{-5}
Inorganic Lead	1.2×10^{-5}	1.2×10^{-5} to 6.5×10^{-5}
Perchloroethylene	5.9×10^{-6}	3.0×10^{-7} to 1.1×10^{-5}
Formaldehyde	6.0×10^{-6}	2.5×10^{-7} to 3.3×10^{-5}
Chloroform	5.3×10^{-6}	6.0×10^{-7} to 2.0×10^{-5}
Acetaldehyde	2.7×10^{-6}	9.7×10^{-7} to 2.7×10^{-5}
Trichloroethylene	2.0×10^{-6}	8.0×10^{-7} to 1.0×10^{-5}
Methylene Chloride	1.0×10^{-6}	3.0×10^{-7} to 3.0×10^{-6}
Asbestos	1.9×10^{-4} (per 100 fiber/m^3)	*Lung*: $11–110 \times 10^{-6}$ (per 100 fiber/m^3) *Mesothelioma*: $38–190 \times 10^{-6}$ per 100 fiber/m^3)

Does the concentration of DEF in ambient air pose a potential health hazard for humans?

The risk for potential health effects from acute and seasonal exposure is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL from the animal studies to the estimated human acute and seasonal exposure dosage. The estimated MOEs for acute and seasonal exposure to DEF in ambient air were greater than 9,000 and 20,000, respectively. In general, an MOE of at least 100 is desirable to allow for extrapolating from animals to humans and for extrapolating from the average person to the more sensitive person in the human population. The estimated risk for carcinogenic effects is the product of its carcinogenic potency and the estimated human annual average exposure dosage. The estimated carcinogenic risk from exposure to DEF in ambient air ranged from 7.5 excess cancer cases per 100 million people to 7.1 excess cancer cases per ten million people. A carcinogenic risk level of less than one excess cancer case per million people is generally considered negligible.

Do any of the degradation products of DEF pose a potential health hazard?

DEF is readily degraded to n-butyl mercaptan in the environment. There was only limited data on the health effects of n-butyl mercaptan. In animals, the acute health effects of n-butyl mercaptan are typical of central nervous system depression, including muscular weakness, lethargy, sedation, and cyanosis. In addition, n-butyl mercaptan appears to cause ocular and respiratory irritation. n-Butyl mercaptan caused destruction of red blood cells through the formation of methemoglobin (an inactive form of hemoglobin) in at least one species. Microscopic changes in the liver, kidney, and lungs were also seen. Reduced maternal weight gain, increased abortions, and fetal malformations were seen in pregnant mice exposed to n-butyl mercaptan. No reproductive, chronic or genetic toxicity studies were available for n-butyl mercaptan. All of the developmental, reproductive, and chronic toxicity studies for DEF exposed animals by the oral route. Some of the effects observed in these oral studies, such as anemia, may be due to n-butyl mercaptan that is formed in the gut from the hydrolysis of DEF.

Some of the symptoms reported in humans in communities near cotton fields, especially the ocular and respiratory irritation, may be due to n-butyl mercaptan. However, no reliable air monitoring data for n-butyl mercaptan was available; therefore, MOEs could not be estimated for n-butyl mercaptan. The highest reported daily average air concentration for n-butyl mercaptan (28.6 $\mu g/m^3$ or 7.75 ppb) is more than eight-fold below this reference exposure level, but is above the odor threshold for n-butyl mercaptan in humans (0.01 to 1.0 ppb). Offensive odors can trigger symptoms in humans, such as headaches and nausea, through indirect physiologic mechanisms such as innate odor aversion, stress-induced illness, or aggravating underlying medical conditions.

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Evaluation of DEF as a Toxic Air Contaminant
April 13, 1999